Guidance on the Content and Format of

Premarket Notification [510(k)] Submissions for

Testing for Skin Sensitization To Chemicals In Latex Products

DRAFT

This guidance document is being distributed for comment purposes only.

Infection Control Devices Branch

Division of Dental, Infection Control and General Hospital Devices

Office of Device Evaluation

Center for Devices and Radiological Health

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[Note: Comments should be submitted for agency consideration within 30 days of release of this document on the internet by writing to Chiu S. Lin, Ph.D., Food and Drug Administration, CDRH, HFZ-480, 9200 Corporate Boulevard, Rockville, MD 20850 or by e-mail to oxl @ cdrh.fda.gov. For questions regarding the use or interpretation of this guidance, also contact Chiu S. Lin, Ph.D. at (301) 443-8913.]

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Center for Devices and Radiological Health

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DRAFT

TESTING FOR SKIN SENSITIZATION TO CHEMICALS IN LATEX PRODUCTS

PROPOSED GUIDANCE DOCUMENT

A. PURPOSE

This document is intended to provide to manufacturers and FDA personnel, guidance for the preparation and evaluation of 510(k) submissions for natural rubber latex (NRL) medical devices with a labeling claim:

(a) for reduced potential to induce sensitization to natural rubber latex chemical additives in unsensitized individuals or;

(b) for reduced potential to induce reaction to natural rubber latex chemical additives in sensitized individuals.

In addition, this document describes testing recommended to support these claims.

B. BACKGROUND

The increased use of natural rubber latex (NRL) medical gloves and other natural rubber latex medical devices, that coincided with the emergence of HIV infection, resulted in the increased prevalence and intensity of adverse reactions to NRL. There are three distinctive types of adverse reactions to NRL that differ in mechanisms of induction as well as in clinical manifestations. These reactions include irritation, delayed hypersensitivity (Type IV allergy) and immediate hypersensitivity (Type I allergy). The major distinctions among the three types are that: a) irritation is a nonimmunologic response with symptoms described as irritant contact dermatitis; b) Type IV allergy is a cell-mediated immunological reaction resulting in allergic contact dermatitis that develops 1 to 4 days after the exposure; and c) Type I allergy is an antibody-mediated reaction occurring immediately, usually within minutes after the exposure. While clinical manifestations of irritation and Type IV allergy are limited to skin reactions, clinical symptoms of Type I

allergic reactions may range in severity from local skin reactions, defined as contact urticaria, to life-threatening anaphylactic reactions. Irritation can be induced by water, powder and chemicals, while Type IV allergy is predominately induced by the residual chemical additives (thiazoles, thiurams and carbamates) on the finished NRL products. Type I allergy is primarily caused by NRL proteins remaining on the finished products.

Although the term Type IV allergy is synonymous to Type IV hypersensitivity, the term Type IV allergy will be used in this document. Both types of allergic reactions to NRL products (I and IV) present serious problems, as the exposure of sensitized individuals to latex medical devices may be either life-threatening (Type I) or career-threatening (Type IV). Although Type I allergy is presently an issue of major concern due to an increase in prevalence and severity of the reactions in the past few years, Type I allergy is not the subject of this document. This guidance document is focused **only** on Type IV allergy to residual chemicals (thiazoles, thiurams and carbamates) on the finished NRL devices. It is important, however, for users of this document, when selecting the human test subject panel, to consider the possibility that some of the healthy test subjects and some of the individuals demonstrating Type IV allergy may also have Type I allergy. Irritation reaction, a nonimmunolgical response, is also not a subject of this document. (Section E.1 and Appendix 1).

Allergy to chemical additives in NRL products has been known for a long time. Efforts were made by industry to alleviate the problem by manufacturing products with reduced levels of chemical additives, which are known to have sensitizing potential. In the past, the label "hypoallergenic" was applied to distinguish such products from the rest of the marketed products. However, with the apparent recent increase in the prevalence and severity of Type I allergy to NRL proteins, the term “hypoallergenic” has been frequently misinterpreted as being related to protein allergy. Such devices, although labeled hypoallergenic, can cause allergic reactions in individuals sensitized to NRL proteins and should not be used by such individuals. Because of the confusion, FDA published in the Federal Register(FR, Vol.62, No. 189, September 30, 1997, pages 51021-51030, “Natural Rubber-Containing Devices; User Labeling”), a rule prohibiting the label claim of "hypoallergenic" on NRL containing medical devices. After the rule becomes effective on September 30, 1998, the manufacturers can utilize this guidance document to

address the labeling options and to conduct appropriate testing to support the new claims regarding: a) reduced potential for inducing sensitization to chemical additives in unsensitized individuals; and b) reduced potential of reaction in individuals sensitized to specific chemical(s).

C. CLAIMS AND TESTING RECOMMENDATIONS

Firms wishing to make a claim regarding the reduced potential of chemical sensitization or reduced reaction-inducing potential of their products in allergic individuals should submit to FDA the recommended testing data for all NRL medical devices as described in the FDA manual "Guidance for Medical Gloves: A Workshop Manual" (FDA 96-4257), which include skin irritation and dermal sensitization studies in animals. In addition to these basic biological evaluations, the recommendations of this guidance document should be followed to support the following proposed claims:

Proposed Labeling Claim 1.

Testing has shown that this product probably will not cause a contact skin reaction in people who are not known to be sensitized to the chemical additives in natural rubber latex products.

CAUTION: Do **not** use this product if you have a known chemical or protein sensitivity. This product has **not** been tested for protein sensitization.

Supporting Test Data:

A negative skin sensitization study (Modified Draize-95 Test) on a minimum of 300 nonsensitized human subjects, as described in Section E below.

Proposed Labeling Claim 2.

Testing has shown that this product is less likely than many other types of natural rubber latex products to produce an allergic contact skin reaction in persons with known contact sensitivity to [name of chemical sensitizer(s)].

WARNING: Do **not** use this product if you have a known protein allergy. This product has not been tested for protein sensitization.

Supporting Test Data:

a) A negative Modified Draize-95 test as recommended for claim 1 above;

b) A negative patch test on 25 individuals who are allergic to the defined major chemical sensitizers present in natural rubber latex products as described in Section F below.

D. ADDITIONAL REGULATORY INFORMATION REGARDING CLAIMS

(1) The NRL products labeled "hypoallergenic" which are presently on the market may, upon removal of the claim from all labeling, remain on the market without the need to supply additional documentation to the FDA.

(2) Manufacturers who intend to market a NRL product, previously labeled "hypoallergenic" with one of the new claims mentioned above, would need to submit a new 510(k) with supporting data from testing described in this guidance.

(3) Applicants who have already submitted data on 200 subjects, using the same procedure described in this guidance, may provide an additional 100 subjects to complete the recommended 300 subjects to satisfy the Modified Draize-95 test.

(4) For new NRL products intended to bear the claims described in this document, a 510(k) should be submitted with data from testing described in this guidance document.

A list of testing laboratories equipped to perform the Modified Draize-95 test on normal subjects is available through the Office of Health and Industry Programs, Division of Small Manufacturers Assistance (DSMA) by telephone #1-800-638-2041 or DSMA FAX ON DEMAND #1-800-899-0381. The partial list of physicians and groups with access to sensitized individuals and equipped to perform testing on sensitized subjects can also be obtained from DSMA.

E. MODIFIED DRAIZE-95 TEST

The purpose of this test is to evaluate whether a finished natural rubber latex (NRL) product contains residual chemical additives that may induce Type IV allergy in the unsensitized general user population. The original sensitization test was developed by John Draize for use with rabbits and later adopted for skin testing in humans. For the purpose of this guidance document, the Modified Draize-95 Test includes additional changes that specifically evaluate the sensitization potential of chemical compounds in finished NRL products. These changes were based on the existing data, past experience and recent knowledge from published literature. See Appendix 1. This test should be used for claim 1 and for initial testing to support claim 2.

E.1. Test Subjects:

Testing should be performed on a minimum of 300 nonsensitized adult human subjects. This sample size provides 95% confidence that all negative results imply that the chemical sensitization potential of the tested natural rubber latex medical products in the user population would be expected to be less than 1.0%.

Protocol

Testing should be performed in at least two environmentally different locations with a minimum of 150 subjects each completing the test.

The criteria for selection of the test subjects should be as follows:

Inclusion

a. Test subjects should be normal volunteers who have documented informed consent.

b. Efforts should be made to provide racial and gender diversity of the test subjects that reasonably reflects the general user population in the U.S.

c. Age of the test subjects should range from 18 to 65 years, and again should reflect, as much as possible, the age distribution of the occupationally exposed population.

Exclusion

a. The test subjects should not have any visible skin disease that might be confused with skin reactions from the test material.

b. The test subjects should not include individuals with any knowledge or indication of existing Type IV allergy to natural rubber latex chemical additives.

c. The test subjects should not include individuals with any indication of existing Type I allergy to natural rubber latex proteins.

d. The test subjects should not include individuals with a history of frequent irritation.

e. The test subjects should not include individuals who were using corticosteroids two weeks before testing, either systemically or topically on the potential test site.

f. Test subjects should not include individuals that have received endogenous or exogenous immunosuppressive treatment.

g. The test subjects should not include pregnant women.

E.2. Procedure:

a. **General -** The study for claim 1 should be conducted in two stages. In the first stage, a population of 50 human subjects(or 25/site) may be tested to evaluate product for the potential to cause irritation or sensitization. If the test product does not indicate a potential for inducing dermal irritation and does not show sensitization capability, the second stage can be initiated on the remaining 250 individuals between the two sites.

   During the induction phase of the study, if a subject tests positive or shows signs of irritation after patch applications, testing on those individuals should be stopped. All cases should be recorded and reported in addition to the 300 subjects in the test panel group. These data would also be necessary for the initial testing of claim 2.

b. **Induction Phase** - A sample of the test article, at least 1 inch x 1 inch in size,(see Appendix 1) is applied to each test subject in the study. Selection of the application site should be according to the ASTM PS77-97 protocol. If multiple testing is performed on the same subject, other test articles being evaluated should not contain the same chemicals as NRL products to avoid potential excessive reaction. The patch should be continuously secured on the edges with a nonreactive adhesive tape. The complete occlusion of the patch is essential.

   The standard test consists of a three week induction period during which nine patches are applied on each Monday, Wednesday, and Friday. The test article is removed and replaced by a new one at the same site every 48 hours for a total of nine changes. The patches applied on Fridays are removed on Mondays.

All skin reactions, if any, should be recorded during this induction phase. If a reaction to an initial induction test patch is observed, the subject should be considered a presensitized individual. A reaction observed after placement of the second patch in the induction phase is generally considered an irritation. In each of these cases, the procedure described in section E.2a would apply. If a local irritation caused by the occlusion material occurs, it should be replaced with the non-irritating one, and the induction patching could be continued.

c. **Rest Period** - At the end of the third week of the induction period, the test article is removed. No test articles are to be applied to the test subjects for the next two weeks.

d. **Challenge Phase** - Two samples of the same test article (challenge patch), 1 inch x 1 inch size are then applied for 48 hours, one to the original test site and another to a virgin site. The test sites are evaluated for the reaction at the time of the patch removal and again two to four days later.

e. **Scoring Criteria**- The suggested scoring criteria are that of the ASTM Provisional Standard PS77-97, “Standard Clinical Method for Repeat Human Insult Patch Testing of Medical Gloves”.

E.3. Data Presentation:

A detailed study report should be submitted in a 510(k), which should include, at least, such items as study protocol, test subject selection, scoring criteria, test results, and interpretation of results. It is suggested that the data be presented separately for each study group of 150 individuals from each of the two test site locations. In order to qualify for the claim of a reduced sensitization potential, all 300 individuals completing the study should exhibit a score value of no more than 1.5, based on the scoring criteria described in ASTM PS77-97. Both presensitized individuals and those presenting irritant reactions identified during the testing, would be excluded from the statistical evaluation. However, data from each such case should be recorded and reported with the data for the 300 nonsensitized test individuals completing the test.

F. PATCH TEST ON SENSITIZED INDIVIDUALS

The purpose of this test is to determine whether a finished natural rubber latex product contains residual chemicals which might cause a skin reaction in individuals who are already allergic to one or more of the following classes of chemicals: thiazoles, thiurams and carbamates. These test data combined with the data from the Modified Draize-95 test described for claim 1, should be used for products to support claim 2.

To obtain test subjects with a prediagnosed allergy of 1+ the recommended test standard is the North American Contact Dermatitis Research Group (NACDRG). The NACDRG standard diagnoses an allergy level of a 1+ reaction after a minimum of two readings, the first at 48 hours and the second reading between days four and seven ("Am. J. Contact Dermatology" 2:122-129,1991). The diagnostic test should be performed up to one month prior to the subject being tested for the NRL product evaluation.

F.1. Test Subjects:

The study should include a minimum of 25 individuals who were positively diagnosed to be allergic to each of the above classes of chemical sensitizers in natural rubber latex products. This sample size provides for 95% confidence that all negative results imply that chemicals on the tested natural rubber latex medical products would be expected to cause reactions in less than 11.3% of sensitized individuals.

The criteria for selection of the test subjects should be as follows:

Inclusion

a. Test subjects should be normal volunteers who have documented informed consent.

b. Efforts should be made to provide racial and gender diversity of the test subjects that reasonably reflects the general user population in the U.S.

c. Age of the test subjects should range from 18 to 65 years, and again should reflect, as much as possible, the age distribution of the occupationally exposed population.

d. Individuals who have a prediagnosed allergy of a 1+ reaction to the chemical sensitizers in the NRL product to support claim 2.

Exclusion

a. The test subjects should not have any visible skin disease that might be confused with skin reactions from the test material.

b. The test subjects should not include individuals with any indication of existing Type I allergy to natural rubber latex proteins.

c. The test subjects should not include individuals who were using corticosteroids two weeks before testing, either systemically or topically on the potential test site.

d. Test subjects should not include individuals that have received endogenous or exogenous immunosuppressive treatment.

e. The test subjects should not include pregnant women.

F.2. Test Procedure:

A 1 inch x 1 inch sample of the same test article as described in Section E is applied to each of the 25 human subjects who were previously diagnosed to be allergic to any or all of the three classes of known chemical sensitizer(s), thiurams, carbamates and thiazoles, in NRL products.

In this test procedure the patch is applied with all edges continuously secured with non-reactive adhesive tape for 48 hours. Complete occlusion of the patch is essential. If the test article causes discomfort to the individual, it should be removed earlier. The test sites are evaluated at the time of the patch removal and again two to four days later.

F.3. Data Presentation:

A detailed study report should be submitted in a 510(k),which should include, at least, such items as study protocol, test subject selection, scoring criteria, test results, and interpretation of results. The sensitivity level score for each allergic subject before involvement in the testing should be recorded and reported with the test results. In case of allergy to more than one chemical, the score should be reported for each chemical. All tested individuals in this group should present negative results (a score of less than 1.5 based on the ASTM Standard PS77-97) as a prerequisite for the claim of reduced reaction-inducing potential.

G. INVESTIGATIONAL DEVICE REQUIREMENTS:

This guidance document applies to the NRL medical devices, which have gone through additional manufacturing processes to reduce levels of residual chemical additives, and have shown negative results in the irritation and dermal sensitization studies in animals. Therefore, the level of risk to the nonsensitized subject during a skin patch test would be considered nonsignificant risk. In addition, the studies performed on sensitized subjects with a patch test of NRL products should be nonsignificant risk studies because the products, as a prerequisite, should have passed the Modified Draize-95 test.

A nonsignificant risk device study, under IDE regulations (CFR 812), requires an institutional review board approval and affords the patient informed consent. Studies conducted in foreign countries are not subject to the IDE regulations, although the FDA recommends that they be conducted according to IDE provisions, or at a minimum be in compliance with the Helsinki Declaration.

H. FOR FURTHER INFORMATION OR QUESTIONS REGARDING THIS DRAFT GUIDANCE PLEASE CONTACT:

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APPENDIX 1.

The Modified Draize-95 test procedure described in this document is in general accordance with the provisional ASTM standard, ASTM PS77-97, “Standard Clinical Method for Human RIPT of Medical Gloves” with the following exceptions:

1. The size of the test patch:

The size of the test patch specified in this guidance document is 1 inch x 1 inch rather than 2cm x 2cm as in the ASTM PS77-97. Based upon the published data and previous practice using the Draize test, sensitization with 10 patches, sized 1 inch x 1 inch, appears to provide an appropriate and reliable indication of the sensitization potential of tested products. The patch size may not be critical in cases where a defined dose of the test chemical is added to the patch. However, in this case, where the patch itself is a test article, its size actually represents the exposure dose. Thus, reduction of the patch size from 1 inch x 1 inch to 2cm x 2cm, would result in the reduction of exposure dose to almost 60% of the dose previously used in testing gloves for the “hypoallergenic” claim. Because no valid scientific data exist at this time to support such a reduction in the exposure dose without compromising sensitivity of the test, we propose to continue testing with the 1 inch x 1 inch patch size. We agree, however, to reduce the number of patch applications from 10 to 9 patches. Although this reduces the exposure dose by 10%, it has been accepted for this guidance as a way to lower the cost of testing.

2. Irritation:

According to the ASTM PS77-97, a mild irritation is acceptable for products that pass the sensitization test and would have claim(s) stated in the 510(k) application. FDA disagrees with this statement. FDA believes that whether a NRL device, which exhibits only irritation reaction, should be ignored or not, is a regulatory question and should not be a part of the interpretation of sensitization test results. As recommended in the “Guidance for Medical Gloves: A Workshop Manual” (FDA 96-4257), all NRL products cleared for the market must pass biocompatibility testing, which includes animal sensitization and irritation tests. As stated in the exclusion criteria in section E.1., individuals who may have highly sensitive skin and a tendency to develop irritation caused by factors such as detergents, water or powder will not be included in the study.

FDA is recommending that manufacturers provide a detailed report that includes those subjects demonstrating a positive reaction during the induction phase, so that the potential hazard of the testing and or product can be evaluated.

3. The number of test subjects:
The size of test subject panels for both healthy and already sensitized individuals was based on the previously described statistical considerations, the expert panel at a workshop "Contact Sensitivity to Natural Rubber Latex" organized by the FDA in 1994, and supported by the September 1997 General Hospital and Personal Use Devices Advisory Panel's recommendations.